American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Review Article

Chemical Stability of Pharmaceutical Organic Compounds

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To Cite This Article: *Topwe Milongwe Mwene-Mbeja . Chemical Stability of Pharmaceutical Organic Compounds. Am J Biomed Sci & Res. 2019 - 6(1). AJBSR.MS.ID.000984. DOI:* 10.34297/AJBSR.2019.06.000984.

Received: September 23, 2019; **Published:** October 30, 2019

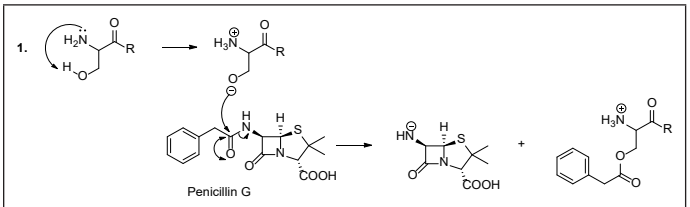
Abstract

According to the reaction conditions, medicines or pharmaceutical organic compounds can be altered via hydrolysis or elimination reactions. They can also degrade through isomerisation, oxidation or polymerization. This review aims to show the reaction mechanisms related to the stability of medicines. In that context, mechanisms are useful in order to explain the formation of products into the chemical reaction medium. When medicines are in an inadequate reaction medium, they disintegrate accordingly. Therefore, it is very important to understand the conditions which modify the stability of medicines so that to identify means to ensure their stability. Indeed, the chemical or physical degradation can alter the therapeutic efficiency of a medicine and it can lead to the production of undesirable products.

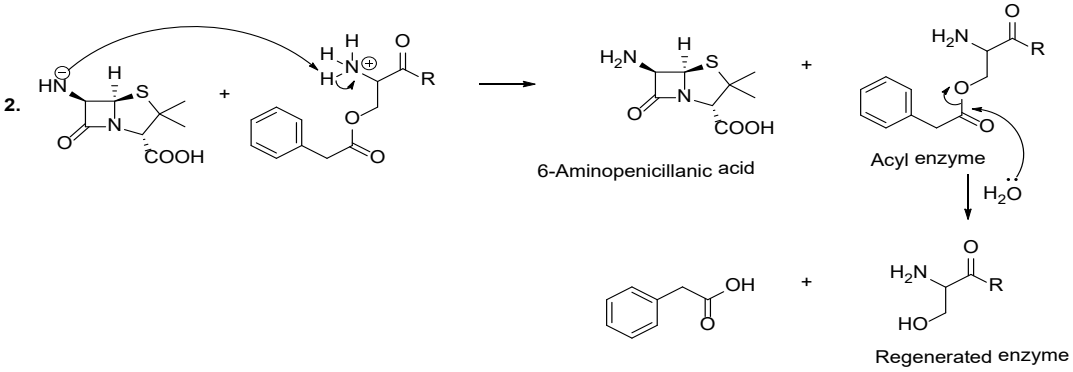
Keywords: Chemistry; Medicine; Degradation; Mechanisms

Penicillin

It has been reported that hydrolytic enzymes such as penicillin acylase, isolated from *d'Echerichia coli*, is able to catalyze the hydrolysis of natural penicillin to produce 6-aminopenicillanic acid. This acid is an important intermediate in the semi-synthetic preparation of antibiotics [1-7]. Experimental observations and structural studies of the enzyme showed that the serine hydroxyl group is transformed into an ester group (Scheme 1A) [1-7]. In other words, the serine hydroxyl group, in the enzyme active center, acts as a nucleophile and the enzyme is regenerated by the nucleophile attack on the serine acyl intermediate or acyl enzyme (Scheme 1B).

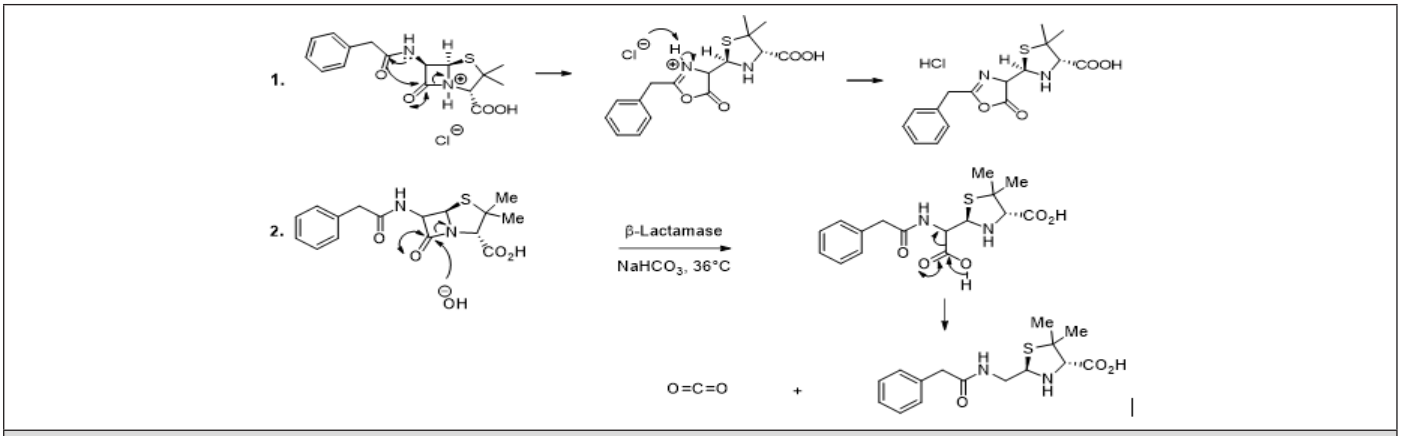


Scheme 1A



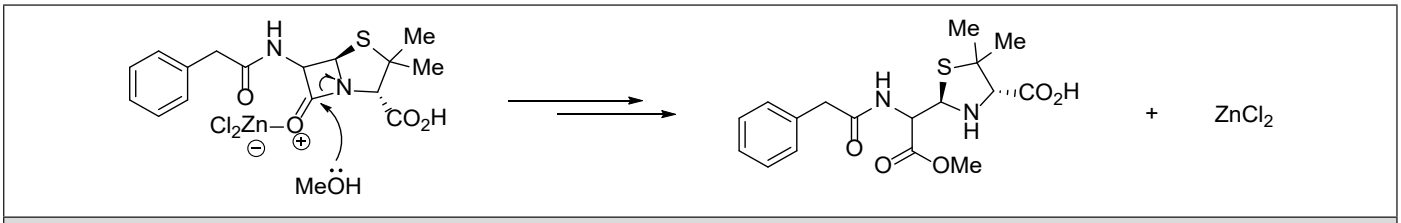
Scheme 1B

It is known that penicillin is generally sensible to acid conditions which catalyze its destruction. The plausible mechanism to explain such decomposition would be due to the proximity of the secondary chain carbonyl group to that of the β-lactam ring. Indeed, the acid reacts with the nitrogen intra cyclic atom to break the amide bond. The breaking is rendered possible by the extra cyclic nitrogen atom, which donates its non-bonded electrons to the secondary chain carbonyl group, which in turn donates its electrons to the β-lactam ring to induce the formation of new ring and the breaking of the β-lactam ring, leading therefore to the complete destruction of the penicillin (Scheme 2, Reaction 1) [1-7]. It has also been observed that penicillinase is a β-lactamase enzyme which destroys penicillin by specifically catalyzing the hydrolysis reaction of β-lactam ring to produce penicillic acid (Scheme 2, Reaction 2) [8].



Scheme 2

The metallic ions such as zinc (II) and cadmium (II) are capable to assist the degradation of four classical penicillin as it happens to amoxicillin, ampicillin, penicillin G and penicillin V in the methanol. In that type of reaction, the Lewis acid activates the lactam ring carbonyl group, and enhances the electrophilic character of the carbon atom of the activated lactam ring carbonyl group, and methanol reacts as nucleophile (Scheme 3) [9].

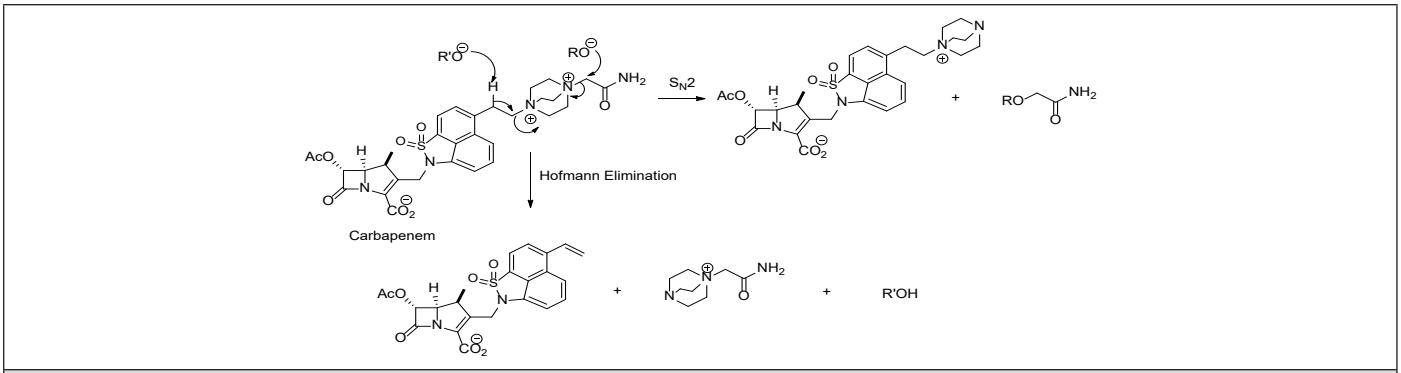


Scheme 3

Carbapenem

Carbapenems are β-lactam antibiotics possessing a very large activity against bacteria and a very high resistance to most β-lactam because of their chemical structures [1-41]. Therefore, they belong to the category of antibiotics used in the first line during severe nosocomial infections [10-50]. These kinds of antibiotics were developed from carbapenem thienamycin, a natural product derived from *Streptomyces cattleya* [10-50] Experimental observations showed that the structure of carbapenem decomposes by Hofmann degradation or nucleophilic substitution reaction (S_N2) (Scheme 4) [10-50].

Atracurium

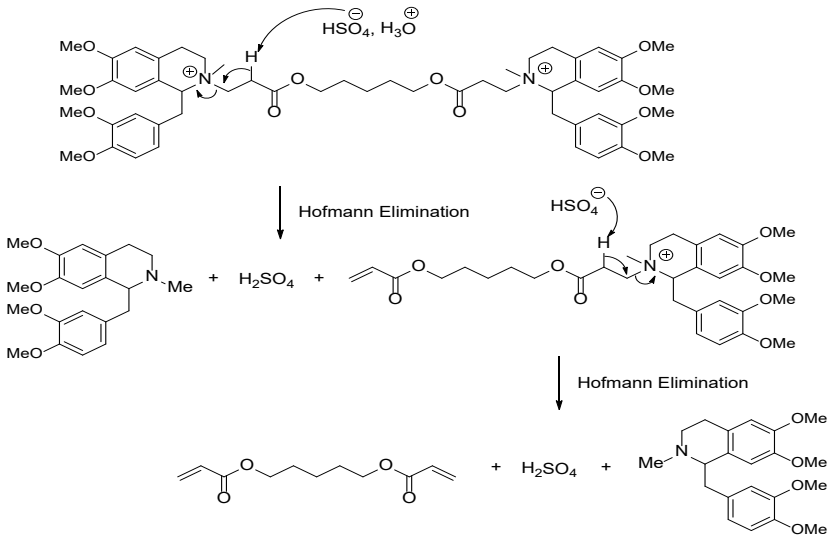


Scheme 4

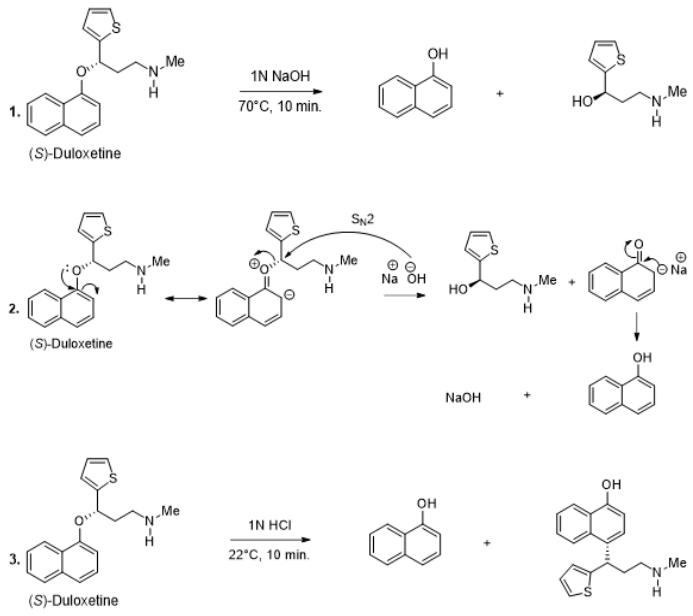
A medicine like atracurium is destroyed by several routes including the Hofmann elimination reaction. This later is a spontaneous degradation which occurs into the plasma and tissues at the human body's normal temperature and pH [10-50]. In this regard, the inhibition of neuromuscular transmission by atracurium is caused by the presence of quaternary nitrogen located at each of the congested ends, which are linked by an aliphatic chain. The structure of atracurium shows two ester groups and an asymmetric centre in each terminal end. The Hofmann elimination reaction commonly known as Hofmann degradation takes place thanks to the presence of two ester groups. Such a reaction was observed at the two ends of atracurium (Scheme 5) [10-50].

Duloxetine

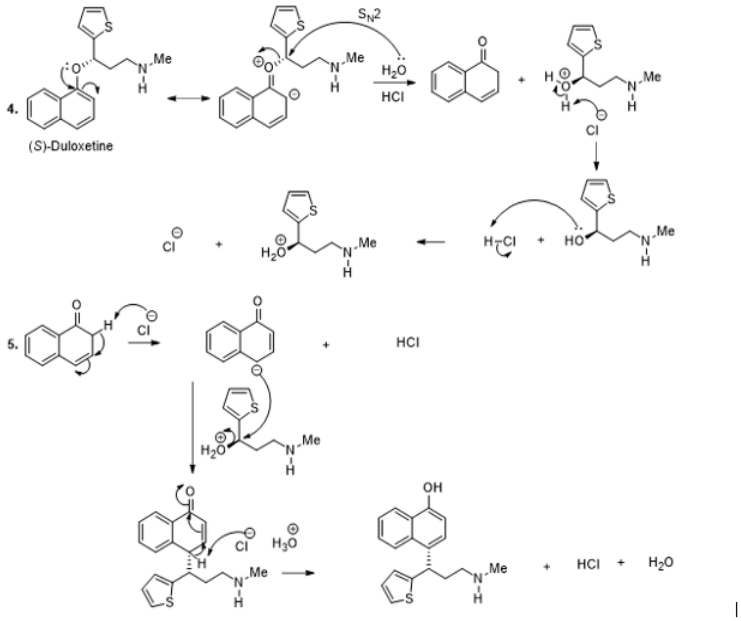
Duloxetine is a solid organic substance slightly soluble into water. This medicine is used to treat the depression and generalized anxiety disorder. It can be used to relieve urinary incontinence. The stability of this medicine depends on the storage conditions, chemical properties, and its impurities. In that perspective, experimental observation showed the disintegration of duloxetine, under alkaline conditions, to corresponding products as naphthol [51]. The plausible mechanism to explain the disintegration products involves the electronic doublet of the duloxetine oxygen atom. In other words, the delocalisation of the electronic doublet of the oxygen atom leads to the generation of two forms of resonance. The action of the base upon the ionic intermediate compound facilitates the disintegration of the medicine and a water molecule permits the formation of naphthol (Scheme 6, reaction 2). On the other hand, it has been observed that under acidic conditions, the degradation product is not naphthol (Scheme 6, reaction 5) [51].



Scheme 5



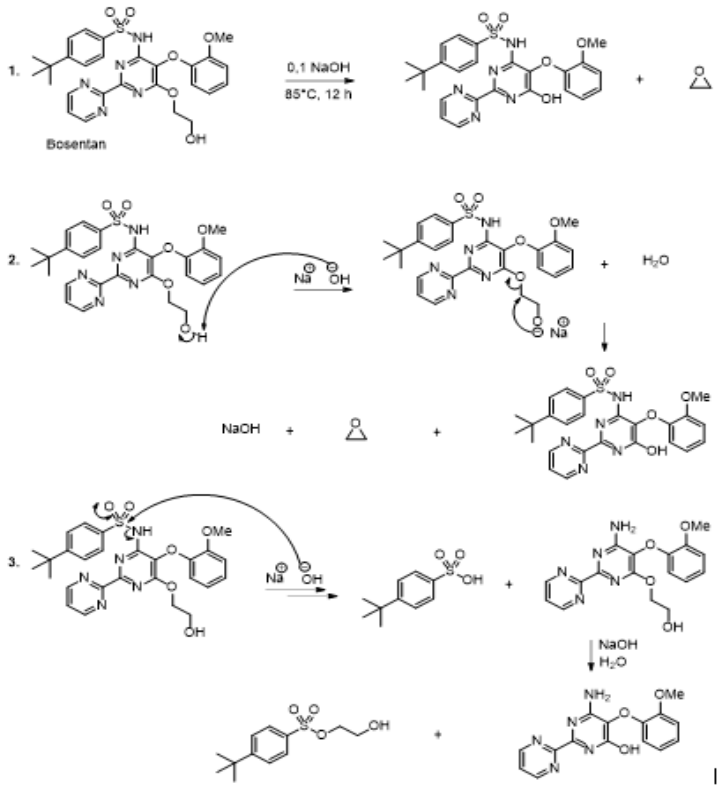
Scheme 6A



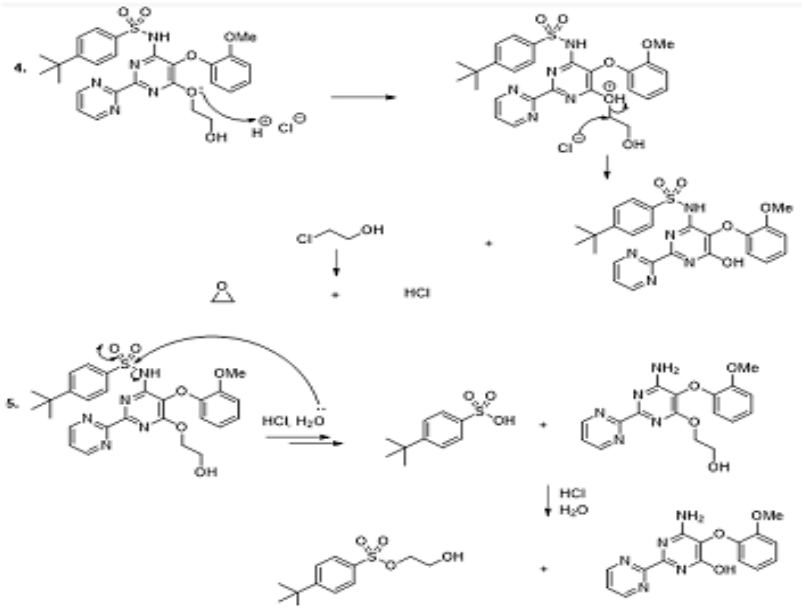
Scheme 6B

Bosentan

Bosetan is a medicine used to treat pulmonary hypertension, chronic heart weakness and Raynauld syndrome. 56 It is one of the latest cardiovascular medicines [52-54]. The experimental observations showed that bosentan is sensible to acidic and alkaline conditions, and the degradation products are the same in acidic or alkaline environment [56]. In this context, the proposed reaction mechanism, in alkaline medium, involves the removal of the acidic proton from the primary alcohol by the base. This alkali action facilitates the elimination of the leaving group due to the nucleophilic attack by the resulting alcoholate ion. Therefore, the hydroxyl group attached to the aryl ring and the epoxide was formed into the medium reaction (Scheme 7, reaction 2).



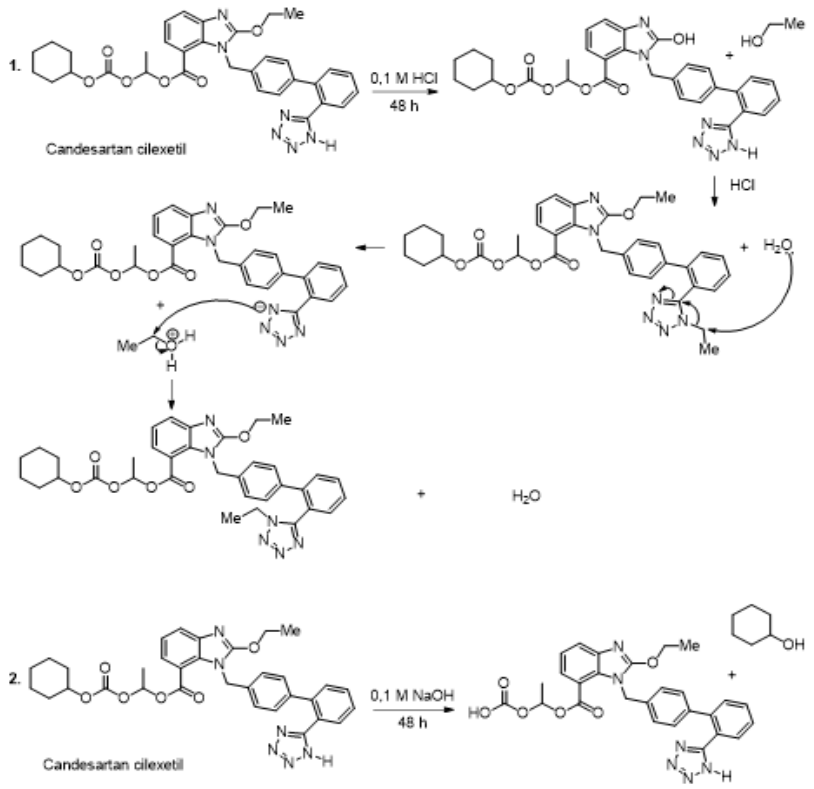
Scheme 7A



Scheme 7B

In the acidic conditions however, the hydrolysis begins by the protonation of the ether oxygen. This step is followed by the chloride ion nucleophilic attack to generate phenol and 2-chloroethanol. The latter can spontaneously cyclize to produce the epoxide and hydrochloric acid (Scheme 7, reaction 3). The amide bond was also hydrolyzed in alkaline medium as well as in acidic environment (Scheme 7, reaction 3). The authors observed also that the oxidation of bosentan by hydrogen peroxide (30 %) took place for 24 hours at the room temperature, and it produced identical compounds as in the case of hydrolysis conditions. This kind of chemical behavior of bosentan was explained by the acidic character of hydrogen peroxide (Schema 7). It was observed that this medicine is stable in water [56].

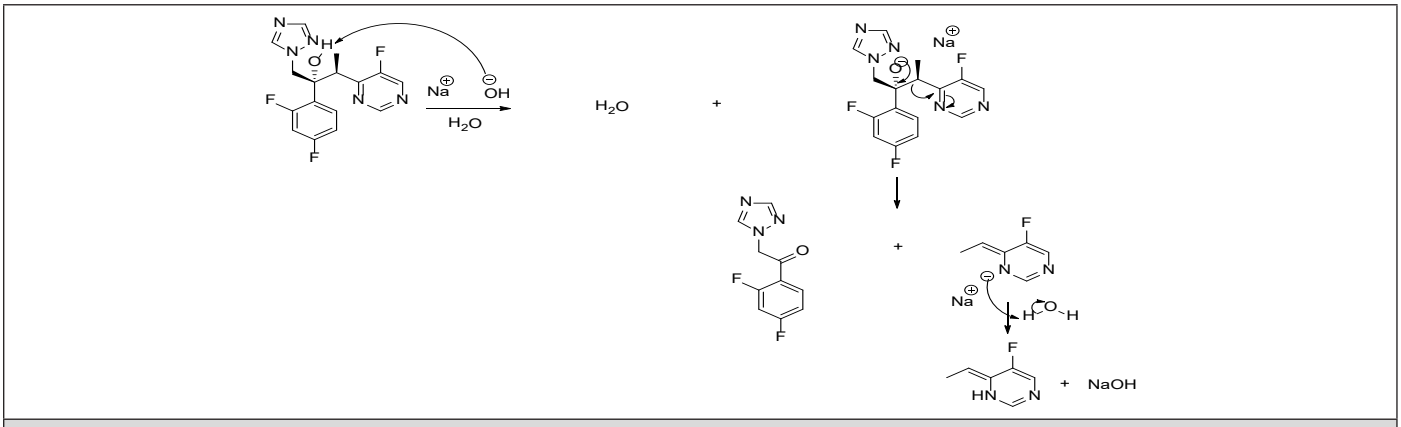
Candesartan cilexetil



Scheme 8

The candesartan cilexetil is a medicine utilised to treat high blood pressure. It reacts with the angiotensin II receptors or proteins, and by doing so it blocks the ability of the angiotensin II, which increases the blood pressure in the arteries. This medicine is not stable in the hydrolysis as well as in oxidation conditions. Indeed, the experimental observations showed that, during 48 hours, the medicine was decomposed and the authors observed identical degradation products in the aqueous acidic medium (0,1M HCl), aqueous medium (H2O), and the presence of hydrogen peroxide (0,10 % H2O2) (Scheme 8, reaction 1). In contrary, the alkaline conditions (0,1M NaOH), for 48 hours, generated one impurity because the ester group was removed (Scheme 8, reaction 2) [57].

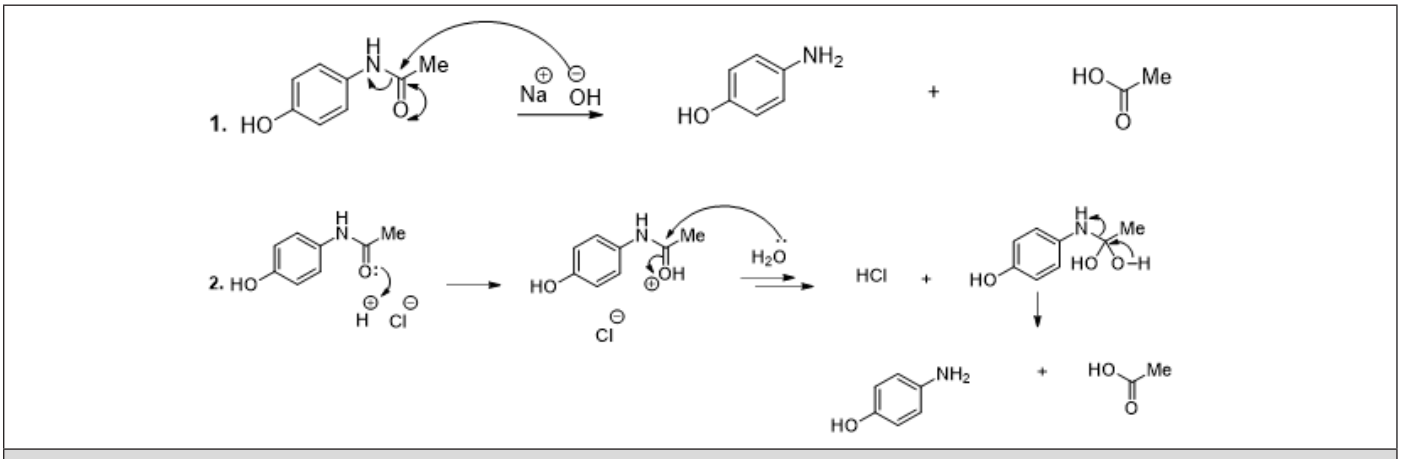
Voriconazole



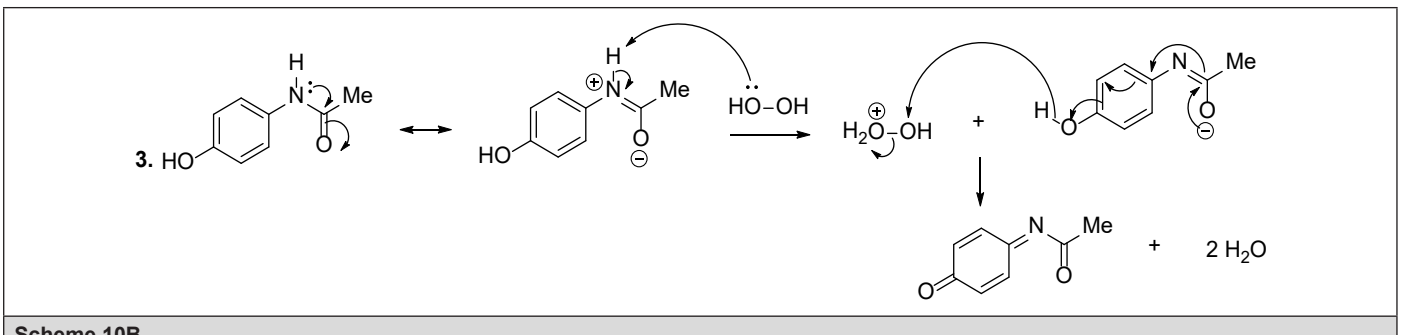
Scheme 9

Voriconazole is a broad-spectrum fungicidal medicine. The study on the chemical stability showed that voriconazole is relatively stable in the solid form but instable when it is dissolved in alkaline medium or in the presence of an oxidant. The formation of the degradation products involves the removal of the tertiary alcohol proton by the base to produce an ionic adduct. The latter decomposes to generate the corresponding ketone and ionic aryl alkene. The action of a molecule of water upon the aryl anion alkene promotes the formation aryl alkene, and the regeneration of sodium hydroxyl (Scheme 9) [58].

Paracetamol



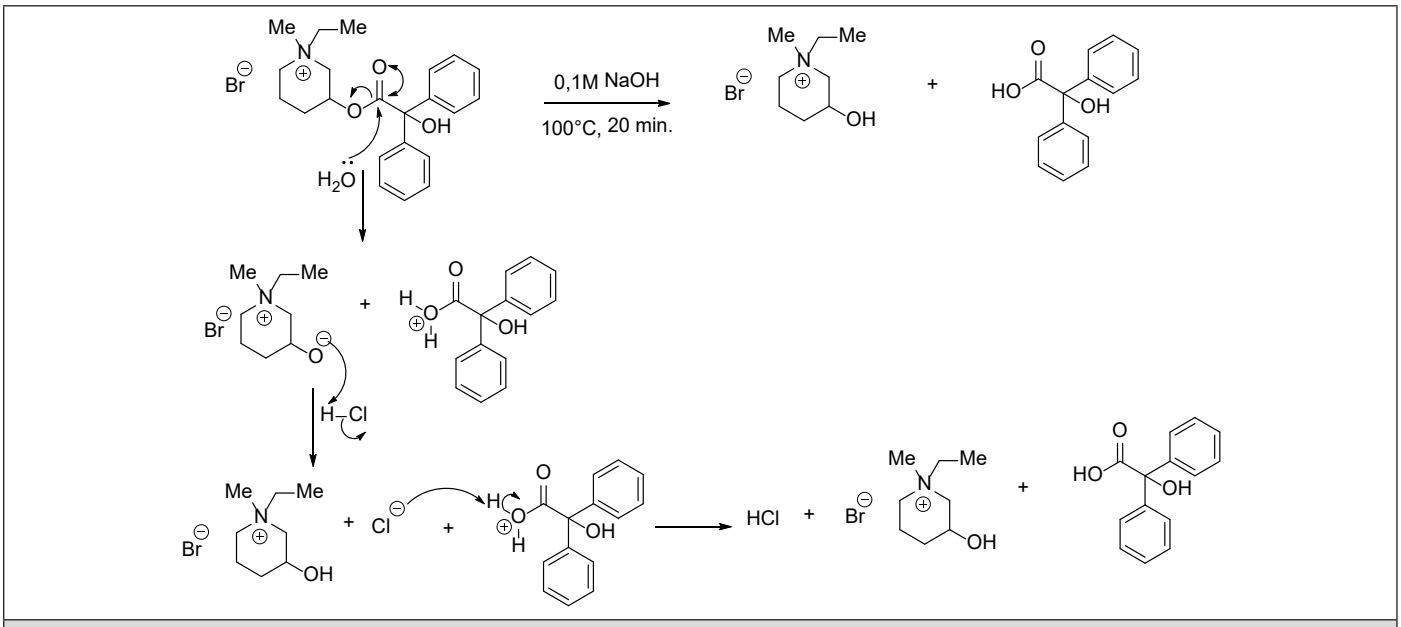
Scheme 10A



Scheme 10B

Therapeutically, paracetamol is a medicine utilised to relieve pain and inflammations.59 In this perspective, it is usually used to relieve headaches and it is incorporated as main ingredient into various flu medications. The disintegration study revealed that paracetamol decomposes substantially under alkaline conditions (Schema 10, reaction 1), acidic (Scheme 10, reaction 2), and in the presence of hydrogen peroxide (Schema 10, reaction 3) [59].

Pipenzolate bromide

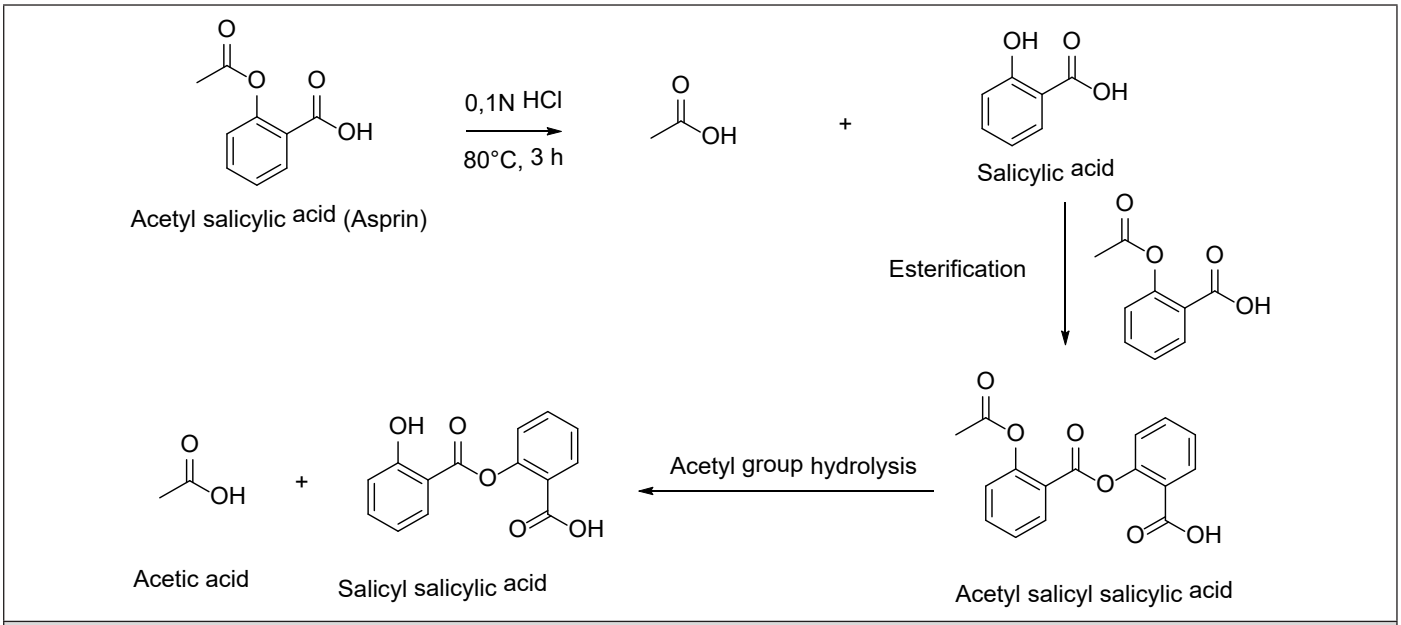


Scheme 11

Pipenzolate bromide is an organic substance with a quaternary ammonium center. From medical point of view, pipenzolate bromide is an anti-muscarinic medicine useful in the treatment of overactive bladder. The chemical structure shows that pipenzolate bromide is an ester typical medicine. Consequently, it is sensible to the hydrolysis catalyzed by an acid or base, and the fragmentation products are identical in the acidic hydrolysis or base hydrolysis (Scheme 11) [60].

Aspirin

Aspirin is a medicine used as an analgesic, against inflammation, and as antipyretic. It is also used to prevent cardiovascular diseases. Structurally speaking, aspirin is an organic compound containing an ester group. That is why, it is sensible to hydrolysis and oxidation conditions. It has been observed that when aspirin is dissolved in aqueous solution containing 0,1N HCl or 0,1N NaOH, it decomposes to corresponding acids (Scheme 12).



Scheme 12

Conclusion

We have illustrated the chemical stability of pharmaceutical organic compounds using hydrolysis, elimination and oxidation reactions. We also proposed plausible mechanisms, as an interesting means, to demonstrate the formation of their degradation products. It is very important to mention that the decomposition of pharmaceutical organic compounds depends on the strength of an acid or a base. In other words, strong acids or bases are well indicated to study the disintegration of medicines.

Conflict of Interest Statement

I declare that I do not have a conflict of interest regarding the publication of this paper.

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